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(54) IMPROVEMENTS IN OR RELATING TO METHODS FOR REDUCING THE DOSES OF BIOLOGICALLY ACTIVE SUBSTANCES WHILE MAINTAINING THEIR BIOLOGICAL EFFECTS

(71) We KOCKUMS CHEMICAL AKTIEBOLAG a Swedish joint-stock company of Nya Agnesfridsvagen 181 S-213 75 Malmo Sweden do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

The present invention relates to biologically active compositions and, more particularly, has for its object, by using a new combination of a biologically active substance and a specific carrier, to provide a method for reducing the required dose of biologically active substance while maintaining its biological effect, i.e. to obtain an improved biological effect. The invention further relates to a biologically active composition for carrying out the method and also the use of such a composition in order to reduce the required amount of biologically active substance when treating a biological system.

The expression "biologically active substance " usually, and in the present context, quite generally is meant to designate compositions containing medicines, killing agents, pesticides, disinfectants (e.g. phenols, chlorinated phenols, such a p-chloro-m-xylenol, tetrabromo o-cresol), biocides, and deodorants.

The use of for instance, pesticides (insecticides, herbicides fungicides, germicides, rodenticides etc.), such as for example DDT (dichlorodiphenyltrichloroethane) has been and still is very extensive, but it has been realized in an ever increasing degree that their use is associated with various risks. Therefore, many countries have regulated the use of pesticides by imposing on them a maximum permissible limit or simply prohibited the use of certain pesticides considered particularly dangerous. However, a prohibition of the use of a pesticide must be weighed against the extant need for the pesticide. In many cases, for instance with regard to DDT, the negative effects of not using the pesticide may seem at least as unfavourable as the risks associated with their use.

To elucidate the problems involved, it may be mentioned that despite pesticide spraying of vegetables, such as tomatoes, the attacks of insects result in damage of a large portion of the tomatoes during distribution. Nevertheless, prohibition of the spraying of tomatoes is being considered with regard to the risks it implies for the consumers. These risks are because the pesticide is present in high concentration on the tomatoes and because of the difficulty of removing the pesticide by washing with water and also because the pesticide penetrates to a certain extent into the tomato itself. Quite naturally, a prohibited spraying of tomatoes would imply considerably reduced production with a reduced supply and higher tomato prices as a result. The same also applies to other fruits and vegetables which are sprayed, such as oranges, apples, pears, lettuce, cauliflower, etc.

Considering that there is already a scarcity of foodstuffs, it is quite unacceptable that foodstuff production, as mentioned above, be further reduced by the prohibition of

pesticide spraying. Consequently, it is highly desirable to find a solution to the problem of the two seemingly contradictory requirements that, on the one hand, attacks of insects and diseases should be controlled by spraying and, on the other hand, health and environmental risks owing to the spreading of pesticide poisons should be reduced.

In accordance with that stated above for pesticides, it is known, as regards medicines, that a plurality of these give rise to undesirable side-effects, for instance gastric haemorrhage when use is made of acetylsalicylic acid, owing to the mucous membrane of the stomach being locally exposed to high concentrations of the agent. On account of biochemical processes in the body organs a higher dosage of the medicine concerned is often required than is in reality needed to produce the specific effect aimed at. Part of the medicine is disintegrated or transformed into other compounds, so-called "metabolites", which in many cases produce the undesired side-effects. In special instances, the necessary dosage may be very close to that which gives rise to toxic effect, particularly in sensitive persons.

Thus, it is evident, also in the case of medicines, that in many cases there is a need to provide a method for reducing, if possible, the required dose of the preparation while maintaining the healing effect in order thereby to reduce or eliminate undesired side-effects. A reduced requirement of the amount of expensive, active medicine substance would of course also entail economical advantages.

That stated above as regards pesticides and medicines also applies to the other biologically active substances mentioned by way of introduction, i.e. it would be valuable both from the economical point of view and from that of environment and health if, in some way or other, the use and spreading of the biologically active substance could be reduced.

The present invention has for its object to provide a solution to the problem outlined above, departing from the fundamental idea that by increasing the activity of the biologically active substance in an appropriate fashion, it would be possible to reduce the quantity required for obtaining a desired result and, thus, attain a reduction or elimination of the undesired negative effects.

According to the method of the invention, the reduction of the amount of biologically active substance necessary for obtaining a specific effect, is realized in that a certain amount of the biologically active substance is combined with a particular carrier in certain defined proportions.

Conventional biologically active preparations are available in the form of liquids or powders, the biologically active constituent, when the active preparation is in powder form, being mixed with a carrier. The prior art preparations differ from the present invention in that they use a much higher amount of active substance, in relation to the amount of carrier compared to the present invention. A further critical distinction is that the "carriers" used in the prior art are used as fillers only, that is the active substance is physically admixed with the carrier and not distributed as an even layer on the carrier as in the present invention. Furthermore the carriers according to the prior art technique mostly have a very low specific surface area of substantially below 50 m^2/g, although silica gel having a surface area of more than 50 m^2/g has been used. Again, in this case the silica gel has been used as a filler and not as a true carrier.

In contrast to the prior art, at the present invention the biologically active substance or a precursor therefor, possible together with further additives, is evenly distributed as a uniform solvent-free layer on an inactive, solid, finely divided inorganic carrier having a surface area of at least 50 m^2/g, the biologically active substance being combined with the carrier in a weight ratio of from $1:10^6$ to 1:1, preferably from $1:10^4$ to $1:10^2$, the dosage of the biologically active substance ranging from 1/2 to 10^{-5} of the minimum dosage required to produce the same biological effect.

(The values of the surface given in this specification are in accordance with the manufacturer's specification. Usually, the surface area is determined by adsorption of N_2 according to the BET-method.)

The invention also provides a method for reducing the amount of biologically active substance required for obtaining a predetermined biological effect, comprising evenly distributing the biologically active substance or a precursor therefor, together with optional additives, on an inactive, solid, finely divided inorganic carrier having a surface area of at least 50 m^2/g in a weight ratio of from $1:10^6$ to 1:1, and selecting the dosage of the biologically active substance to be from 1/2 to 10^{-5} of the minimum dosage conventionally required to produce the same effect. The biologically active substance is preferably distributed on the carrier in a weight ratio of from $1:10^4$ to $1:10^2$. In addition, where carriers have previously been used in the prior art, they have been physically mixed with the active substance and used only as fillers, whereas the importance of the present invention lies in providing a carrier evenly layered with the absolute minimum quantity of biologically active substance required to obtain the desired effect.

Useful inorganic carriers may be chosen from inorganic elements and oxides, acids, salts and polymers thereof. In particular the following types of inorganic carriers should be mentioned: colloidal metal or metalloid oxides, such as alumina and silica; various silicates and other siliceous compounds, such as asbestos, talc, vermiculite, kieselguhr, diatomaceous earth, mica, expanded mica; and carbonates and phosphates of alkaline earth metals, such as calcium carbonate, magnesium carbonate and calcium phosphate. Particularly preferred are the pyrogenic silicas and the alkali metal or alkaline earth metal silicates as will be explained in greater detail hereinbelow.

In a preferred embodiment of this invention, the carrier has a particle size of about 1 to about 250 μm.

In conjunction with a biologically active substance intended for oral intake, such as medicines, too large amounts of inorganic carrier are inappropriate and so, in these cases, the weight ratio of biologically active substance to carrier is chosen to range from 1:1 to 1:20, the amount of biologically active substance ranging from 1/2 to 1/10 of the amount normally required when using the biologically active substance alone.

In other, normal cases, e.g. when using pesticides, it is possible to utilize an increased amount of carrier and a decreased amount of biologically active substance and so, in these cases, the limits are suitably chosen to range from $1:10^6$ to 1:10 and preferably from $1:10^4$ to $1:10^2$ for the weight ratio of biologically active substance to carrier, and from 10^{-1} to 10^{-5} for the amount of biologically active substance as compared with the normally required amount thereof.

Here, the term "inactive" means that the carrier itself does not adversely influence the effect of the biologically active substance. Thus the carrier should not bind the biologically active constituent so firmly as to inhibit its effect. A certain interaction of bonding character may, however, take place between the carrier and the combination of the biologically active substance with optional additives, as will be described in greated detail hereinbelow.

In a preferred embodiment of the invention the inorganic carrier has a surface area of at least 200 m^2/g.

In a further preferred embodiment of the invention the inorganic carrier comprises silica or silicate.

In a particularly preferred embodiment of this invention, the silica is a precipitated silica or a pyrogenic silica prepared by the well-known precipitation or pyrogenic processes. Precipitated and pyrogenic silicas having surface areas of at least about 200 square meters per gram are commercially available.

In the presently most preferred embodiment of the invention, the carrier is a pyrogenic silica which may be obtained in different qualities having a surface area of about 200-1000 m^2/g.

According to the invention it is also important that the carrier used be so modified that it does not itself cause any unbalance in the environment, body or biological system to which the product is supplied. It is possible to acquire silicon dioxide or silicates of different particle sizes and surface areas, it being, however, often necessary to modify these substances with respect to acidity, alkalinity, hydrophilic or hydrophobic character. Experiments have shown that acidic silicon dioxide can be neutralized by the addition of ammonia or ammonium hydroxide, other alkalis, calcium hydroxide, magnesium or barium hydroxides as well as of other metal oxides. Similarly, basic silicon dioxide can be neutralized by the addition of nitric acid, other mineral acids like phosphoric acids, organic acids etc. In this way, the carrier material can be carefully modified so as to suit as well as enrich the particular type of biological system concerned, for instance a certain type of soil. Consequently, it will be appreciated that, while aiming at reducing the dose of biologically active substance, the present invention also acts in favour of the natural balance of environment. Thus, when using pesticides, it is possible to add for instance nitrogen fixing organisms.

In its purest form, the invention involves a combination only of a biologically active substance and a carrier, but as will be readily appreciated and as has also been indicated above, it is of course possible to incorporate various additives, if desirable, without departing from the scope of the invention. However, such additives constitute only secondary constituents, the primary constituents being the biologically active substance and the specific carrier. Various additives may comprise colouring agents and flavourings (including hormonal attractants) in order to give the preparation attractive colour, smell or taste, which may be of importance especially for pesticides. The additives further comprise such agents as have an inhibiting or accelarating effect upon the release of the biologically active substance. Ionically active substances as well as hydrophobic or hydrophilic substances are examples of such agents. The additives further incorporate such common, more or less "inert" additives as diluents and solvents for the biologically active substance. Conventional fillers, such as kaolin, talc, attapulgite, etc., having a surface area of less than

200 m^2/g may also be incorporated as additives. Hormone type agents may also be used as additives. Since a person killed in the art will easily realise still further examples of suitable additives, an extensive enumeration thereof will be superfluous.

For the sake of simplicity the invention will be described in more detail hereinbelow with reference to pesticides and medicines alone as the biologically active substance and silica as the inorganic carrier. The applicability of the invention to the other categories of biologically active substance and other types of inorganic carriers will be easily realized without it being necessry to burden the present application with particular, detailed description for each separate field of use and each type of carrier.

According to the present invention, it has quite surprisingly been discovered that combining a pesticidally active constituent with a carrier of the kind outlined above and in the above-described manner yields a pesticidal composition of considerably improved effect as compared with corresponding conventional pesticidal compositions. In short, the improved effect of the composition according to the invention can be subdivided as follows:

a) The same pesticidal effect as in conventional preparations can be obtained using a considerably smaller amount of pesticidally active constituent, which amount may be as small as 10^{-1} to 10^{-5}, or less, of the amount of conventional agent.

b) The effect according to a) is further enhanced at a lower pesticidal concentration of the composition, that is, at a reduced ratio of pesticidal constituent to carrier.

c) In some cases, the composition according to the invention may give rise to stimulating effects, for instance that in herbicidal compositions undesired growth is inhibited at the same time as desired growth is stimulated to an unexpected extent.

d) The pesticidal composition obtained by the method according to the invention involves minimum health and environmental risks. The reason for this is, on the one hand, that the total amount of pesticide necessary to gain the desired effect is extremely low, in accordance with a) above, and, on the other hand, that the composition can readily be removed by washing from e.g. sprayed vegetables. Besides, owing to the low pesticide content of the pesticidal composition, the risk of the pesticide penetrating into sprayed fruits or vegetables will be almost entirely eliminated.

As to the above-mentioned possibility of readily removing the pesticidal composition of the invention from the treated object, it should be observed here that this property, which is a measure of the strength of the adhesion of the composition to or its bond with the treated material, is important for the total usefulness and effect of the pesticide. Thus, a very strong adhesion to the sprayed object, which may seem advantageous as the pesticide will remain in the contemplated location without being affected by the weather conditions, is unsuitable since it will be difficult or even impossible to remove the pesticide from the object prior to consumption (for instance when the object is a fruit or a vegetable). Moreover, the pesticide may be so firmly bound to the object that its intended effect is reduced, for instance, in that the pesticide is not transferred to the insects attacking a sprayed fruit.

On the other hand, the adhesion of the pesticidal composition to the object should not either be too weak since, in that case, there is a risk that the composition will not adhere at all or, if it adheres, that it will be completely removed from the surfac as a result of the slightest influence, such as rain.

According to the present invention, it has been found that the above inorganic carriers and particularly the silica and silicate carriers imply a very fortunate compromise with regard to the adhesion of the whole pesticidal composition to the sprayed object. It is also possible to modify such compositions according to the invention (by changing the ratio of the active ingredient-containing composition to carrier) so that they may be removed by washing with water at the same time as they adhere sufficiently firmly to the object to maintain the desired biological effect any given length of time. This would prevent the undesired accumulation of active ingredient into the sprayed object (e.g. DDT in tomatoes, Tables 5 and 6).

In addition to varying the proportion between carrier and active ingredient as described above, other changes can also be effected by choosing carriers which have acidic or basic character.

Preferably, the carrier is silicon dioxide or an alkali metal or alkaline earth metal silicate - including double silicates containing alkali metals or alkaline earth metals, or other metals such as aluminum, boron, zirconium and bismuth (e.g. aluminum silicate, magnesium silicate, magnesium aluminum silicate, calcium silicate) - having a specific surface in excess of 50 m^2/g or more. Several of these products are available on the market under different trade names, e.g.

Fluosil®
Cab-O-Sil (Reg. Trade Mark)
Aerosil (Reg. Trade Mark)
HiSil (Reg. Trade Mark)
Zeosil®
Brite Sorb®
Quso®
Manosil (Reg. Trade Mark)
Felite® etc.

The pharmaceutical compositions of this invention can also include a solid or liquid pharmaceutically acceptable non-toxic substance. Such pharmaceutical substances can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred suspending medium when the pharmaceutical composition is administered orally or parenterally. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid additives, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, agar, malt, rice, flour, chalk, silica gel, magnesium carbonate, magnesium stearate, sodium stearate, glycerol mono-stearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water ethanol, and the like. These compositions can take the form of suspensions, tablets, pills, capsules, powders, sustained-release formulations and the like. Suitable formulation techniques for the pharmaceutical products of this invention are described in Remington's Pharmaceutical Sciences by E. W. Martin, the entire disclosure of which is relied upon and incorporated herein by reference. The compositions will contain an effective therepeutic amount of the biologically active compositions of this invention together with a suitable amount of diluent so as to provide the form for proper administration to the host. It will be understood that the pharmaceutical compositions of this invention can be administered orally, parenterally, or topically to mammals.

The invention and the advantages thereof will be further elucidated hereinbelow with the aid of some Examples. When exemplifying pesticides, the following examples are with neccessity limited to a few illustrative pesticides only. For an exhaustive list of pesticides reference may, however, be made to the article of D. Armstrong Lowe and A.R. Stiles, "Pesticides Nomenclature, specifications, analysis, use, and residues in foods", Progress In Standardization:1 WHO, Geneva, 1974, the whole of which is relied upon and hereby included by reference. Particularly useful pesticides and the most effective ratio of pesticide to carrier may be determined by one skilled in the art by simple experimentation.

The biologically active substance can be deposited in a uniform and even layer on the carrier by dissolving the biologically active substance in a solvent therefor, mixing the carrier with the resulting solution, and evaporating the solvent from the resulting mixture. The solvent is selected so that it is inert to the biologically active substance; that is, the solvent must not destroy the biological activity of the substance. Also, the solvent must be capable of being evaporated from the mixture at a temperature substantially below the temperature at which the biologically active substance would be denatured or volatilized or sublime. Evaporation of the solvent should be carried out with very gentle agitation of the mixture, which aids in achieving the even and uniform layer on the carrier. The rate of evaporation can be conveniently controlled by regulating the temperature of the mixture, vacuum applied to the apparatus containing the mixture and evaporation time. These factors will of course be dependent upon the volume of solvent to be removed and will be selected so as to avoid the denaturation or volatilization of the biologically active substance. In the following Examples, methylene chloride was employed as the solvent, and the evaporation time, temperature and vacuum are given. Other solvents can be employed, and optimum conditions determined with a minimum of experimentation.

In the following Examples, use was made of a carrier coated with biologically active substance. In all the cases, the carrier consisted of silica aerogel having a large specific surface area, while the biologically active substance was varied and selected from insecticides, herbicides and medicines. The carrier and the biologically active substance will be described in more detail in the different Examples. The same general method for coating the carrier with the biologically active substance was used in all the Examples, the method being as follows.

A selected amount of carrier according to the invention (300 g) was admixed, under agitation, with methylene chloride (6 liters), or other suitable solvent, for the biologically active substance. Thereafter was added the amount in grams of the biologically active substance which was required in order to bring about the prescribed weight ratio of from $1:10^6$ to 1:1 of biologically active substance to carrier the dosage of the biologically active substance from from $\frac{1}{2}$ to 10^{-5} of the minimum dosage conventionally required to produce

the same effect. Preparations containing the conventional dosage of the biologically active substance were also prepared for comparative purposes. Appropriate additives, such as those earlier indicated, may optionally be added. The resulting mixture was then subjected to the driving off of the solvent by evaporation at a low pressure and temperature (about 20 mm Hg and about 25°C for methylene chloride) for the required period of time (about 20 h) in order completely to eliminate the solvent. The dry product was then gently ground into a powder of a preferred particle size of about 1-250 µm. If such grinding should alter the characteristics of the product, techniques, such as those used in gaschromatography for coating stationary phases on solid supports, can be employed. In principle, the evaporation may be carried out in any appropriate evaporator which permits controlling pressure and temperature in the desired manner. A particularly appropriate apparatus is a rotary flask evaporator of the so-called Rotavapor type. The evaporation should be effected as mildly as possible such that the carrier will be completely coated with biologically active substance, i.e. on its outer surface as well as on the inner parts of the carrier. In case the evaporation is too vigorous, for instance if the temperature is raised to about 35°C when use is made of methylene chloride as solvent, an uneven concentration of biologically active substance will result on the carrier surface.

Although in the following Examples use has been made of the above described method involving coating from solution and evaporation of the solvent, still other methods may be used according to the invention in order to coat the carrier with biologically active substance. Thus, instead of a solution of the biologically active substance, it is possible to use an emulsion thereof, the biologically active substance beng emulsified in a medium which does not serve as a solvent for the substance. The method involving emulsifying the biologically active substance is particularly applicable when the active substance is sparingly soluble in ordinary solvents.

Another, however not as preferred a method, involves directly coating the carrier with the biologically active substance. In this case, the active substance is sprayed directly onto the carrier under vigorous agitation, for instance by means of ultrasonic sound or a fluidized bed in order to maintain the carrier suspended during the application of the active substance.

Yet another coating method involves vapourizing the biologically active substance and condensing the generated vapor on the carrier, whereby there is obtained an even and uniform coating of the active substance on the carrier.

Irrespective of which method is used for coating the biologically active substance on the carrier, the essential and decisive condition for obtaining a satisfactory final product is that the biologically active substance be coated in an even and uniform layer on the carrier.

Example 1

Using the earlier described process of manufacturing a coated carrier according to the invention, three different batches of the carrier (Fluosil®, 200 m^2/g) were manufactured, coated with the insecticide Malathion (S-[1,2-bis(ethoxycarboxyl)-ethyl]-o,o-dimethylphosphorus dithioate) in varying coating contents. The first batch was of the composition 1% Malathion/99% carrier, the second batch was of the composition 0.1% Malathion/99.9% carrier, and the third batch was of the composition 0.01% Malathion/99.99% carrier. Malathion is normally used in an amount of about 0.1 g/m^2.

Twelve open boxes of PVC-plastic were used for the testing of the preparations produced and the inner sides of the side walls of the boxes were covered with rough abrasive paper. The surface of each box thus covered with abrasive paper amounted to 0.05 m^2. The rough abrasive paper coated surfaces of the boxes were then sprayed with 15 ml of suspension in distilled water of the above preparations in various coating amounts, as will appear from Table 1. A non-sprayed thirteenth box was used as check box.

Twenty live wood ants were then placed in each of the boxes sprayed with insecticide and in the check box, and the upper sides of the boxes were covered with a fine-mesh net to prevent the ants from escaping. The boxes were then checked once a day for one week with regard to the number of dead ants in each box. The results are given in Table 1.

From Table 1 it will appear that the pesticide according to the invention is extremely effective also when used in very low contents.

Example 2

To show the superior effect of the pesticide according to the invention, comparative tests were carried out with the insecticide Propoxur (2-isopropoxyphenyl-N-methylcarbamate) as marketed under the trade name Baygon® (available from Bayer Agro-Kemi AB, Malmö, Sweden) and as applied on a carrier with a high surface area (Fluosil®, 200 m^2/g). The different preparations for the tests were as follows:

1) Conventional composition comprising 1% Propoxur on a carrier (Baygon®), 2) 0.1%

Propoxur on Fluosil®-carrier, and 3) 0.01% Propoxur on Fluosil®-carrier. Of each preparation, suspensions in distilled water were prepared of three different concentrations as stated below.

1. Conventional composition (Baygon®)

500 mg was finely comminuted in a mortar and suspended in 50 ml distilled water. The suspension was divided into the following part quantities:

a) 14 ml without further dilution,
b) 7 ml suspension + 7 ml distilled water, and
c) 1.4 ml suspension + 12.6 ml distilled water.

2. 0.1% Propoxur on Fluosil®-carrier

5 g Propoxur-coated carrier was finely comminuted in a mortar and suspended in 100 ml distilled water. The suspension was divided into the following part quantites:

a) 28 ml suspension without further dilution,
b) 14 ml suspension + 14 ml distilled water,
c) 2.8 ml suspension + 25.2 ml distilled water.

3. 0.01% Propoxur on Fluosil®-carrier

5 g Propoxur-coated carrier was finely comminuted in a mortar and suspended in 100 ml distilled water. The suspension was divided into the following part quantities:

a) 28 ml suspension without further dilution,
b) 14 ml suspension + 14 ml distilled water,
c) 2.8 ml suspension + 25.2 ml distilled water.

The above nine different part quantity suspensions prepared were used for the internal spraying of nine plastic boxes the walls and bottoms of which had a total surface of 0.07 m^2. Rough abrasive paper had been secured both to the walls and to the bottoms in order that the sprayed-on insecticide suspension should not flow off. A tenth box was not sprayed but used as check box.

TABLE 1

Box No.	Preparation	Sprayed amount (g/m^2) Insecticide+ Carrier	Insecticide	Sprayed amount in total Insecticide + Carrier (mg)
1	1% Malathion/99% Carrier	100	1.0	5000
2		10	0.1	500
3		1	0.01	50
4		0.1	0.001	5
5	0.1% Malathion/99.9% Carrier	100	0.1	5000
6		10	0.01	500
7		1	0.001	50
8		0.1	0.0001	5
9	0.01% Malathion/99.99% Carrier	100	0.01	5000
10		10	0.001	500
11		1	0.001	50
12		0.1	0.00001	5
13	---	-	-	-

	Number of dead ants						
Day	1	2	3	4	5	6	7
0	20	20	20	20	20	20	
0	20	20	20	20	20	20	
0	11	18	19	20	20	20	
0	12	16	16	18	19	20	
0	20	20	20	20	20	20	
0	12	20	20	20	20	20	
0	11	14	18	20	20	20	
0	6	14	17	19	20	20	
0	9	16	20	20	20	20	
0	8	12	18	19	20	20	
0	12	17	20	20	20	20	
0	11	14	17	18	18	19	
0	3	5	9	12	14	16	

Thirty wood ants were placed in each of the ten boxes and the percentage proportion of dead ants in the boxes was observed after 20 h, 44 h and 72 h.

The test results are indicated in Table 2 from which appears that the preparation according to the invention was more effective than the conventional preparation, and that, in comparison with the conventional preparation, an equally good or better effect was obtained using a smaller amount of the preparation according to the invention. It should be specifically observed that with the same total amount of sprayed active substance of the preparation according to the invention an enhanced effect can be attained with the preparation having a lower content of active substance. Thus, the total amount of active substance sprayed was the same for boxes 1, 4 and 9 but for box 9 which was sprayed with a suspension of 0.01% Propoxur on a carrier, twice as large a proportion of dead ants was observed after 20 h as compared with box 4 and box 1. After 72 h, 90% of the ants in box 9 were dead while in box 4 80% of the ants were dead and in box 1 only 50%.

TABLE 2

Box No.	Prepara-tion	Volume of sprayed solution (ml)	Conc. of sprayed preparation (g/m^2)	Sprayed total amount (mg) Preparation	Active Substance	Dead ants (%) after 20 h	44 h	72 h
1	1c	14	0.2	14	0.14	10	30	50
2	1b	14	1	70	0.7	20	70	90
3	1a	14	2	140	1.4	10	80	80
4	2c	28	2	140	0.14	10	60	80
5	2b	28	10	700	0.7	10	50	90
6	2a	28	20	1400	1.4	20	90	100
7	3c	28	2	140	0.014.	5	20	50
8	3b	28	10	700	0.07	20	50	70
9	3a	28	20	1400	0.14	20	90	90
10	-	-	-	-	-	20	20	20

Example 3

In this Example, experiments were conducted to ascertan the adhesion and penetration of the insecticide DDT (dichlorodiphenyltrichloroethane) on tomatoes when sprayed, respectively, with pure (100%) DDT, that is, not applied as a coat on a carrier, and DDT applied in varying contents as a coat on a carrier according to the invention. The carrier according to the invention consisted, as in the earlier Examples, of silica aerogel having a specific surface of about 200 m^2/g, and this carrier was coated with DDT (in the same way as earlier described and used for the coating of the carriers in the earlier Examples) for making preparations of the composition 10% DDT/90% carrier and 1% DDT/99% carrier, respectively. The three DDT-preparations were suspended in distilled water and the suspensions were then sprayed onto untreated, green tomatoes in boxes of the dimensions 2 dm × 2 dm. The amounts sprayed will appear from Table 3.

TABLE 3

Box No.	Preparation	Sprayed total amount DDT + carrier (mg)	Sprayed total amount of active substance (mg)
1	100% DDT	-	80
2	"	-	8
3	"	-	0.8
4	10% DDT/ /90% carrier	800	80
5	"	80	8
6	"	8	0.8
7	1% DDT/99%-	800	8
8	" carrier	80	0.8
9	"	8	0.08

The tomatoes thus treated were then analysed with regard to DDT prior to and after rinsing the tomatoes under tap water for the removal of the insecticidal preparation sprayed on to them. The results of the analyses are indicated in Tables 4 and 5.

It appears from Table 4 that the insecticide penetration diminished most significantly with the use of the preparation according to the invention as compared with the use of DDT only. It appears from Table 5 that the sprayed preparation according to the invention is completely removed by washing with water, whereas a considerable amount remains in conventional spraying with DDT only.

TABLE 4

DDT residues in tomatoes sprayed with DDT and DDT applied as a coat on carrier (200 m²/g)

Test No.	Preparation	Spraved amount mg/kg in total	Spraved amount mg/kg active substance	DDT content in tomatoes * mg/kg (=ppm)
1	DDT (100%)	8	8	0.284
2	DDT (10%) + carrier (90%)	80	8	0.143
3	DDT (1%) + carrier (99.0%)	800	0.085	
4	DDT (100%)	0.8	0.8	0.342
5	DDT (10%) + carrier (90%)	8.0	0.8	0.107
6	DDT (1%) + carrier (99.0%)	80	0.8	0.062

* After extraction and purification the p-p'DDT content in the extracts was gas-chromatographically and thin-layer chromatographically examined. Gas chromatography was effected with the use of electron-capture detector and mixing column (SF96 and QF1 on Chromosorb W.H.P.).

TABLE 5

The effect of rinsing with water on the DDT content in tomatoes sprayed with DDT and DDT applied as a coat on carrier (200 m^2/g)

Test No.	Preparation	Sprayed amount mg/kg in total	Sprayed amount mg/kg active substance	DDT residue in tomatoes mg/kg (=ppm) Experiment I	Experiment II
1	DDT (100%)	80	80	0.118	0.069
2	DDT (10%) + carrier (90%)	800	80	<0.024	<0.005
3	non-sprayed (check)	0	0	<0.005	<0.005

Example 4

This example is intended to show the effect to the invention when the pesticide is a herbicide. As herbicide, use is made of Simazin (N,N'-diethyl-6-chloro-S-triazine-2,4-diamine) on the one hand, in the form of a powder which contained 50% of active substance (this composition is marketed under the trade name Gesatop Reg. Trade Mark, normally used in an amount of about 0.15 to 0.25 g/m^2 active substance, by AB Plantex, Södertälje, Sweden) and, on the other hand, applied as coats in different contents to silica aerogel carriers having large specific surfaces of about 300 m^2/g. The Simazin/carrier preparations with large surfaces were made in the same way as earlier described and as used for the production of the insecticide/carrier preparations in the earlier Examples. Tests on three different Simazin preparations were made, viz:

A. Gesatop (Reg. Trade Mark) (50% active substance)

B. 20% Gesatop® on 80% carrier with large surface, that is, the content of active substance = 10%

C. 2% Gesatop® on 98% carrier with large surface, that is, the content of active substance = 1%.

In addition to the herbicide preparations described above, 13 boxes having a bottom surface of about 0.25 m^2 were put in order by filling with earth and sowing of radish, spinach, lettuce and grass seeds in each box.

After being prepared, the boxes were sprayed with different amounts of water suspensions of the above-mentioned preparations as is indicated in Table 6. One box (box No. 13) was left unsprayed to serve as a check. The different boxes were observed during approximately two months with regard to growth, both of weed and vegetables. It was established that, except for box 13 (check), all boxes were free from weed, and that the vegetables in the sprayed boxes showed a greatly varying growth. The growth of the vegetables is indicated in Table 6. As a supplement of the growth values in Table 6, it may be mentioned that the general visual impression of the growth in the boxes was that in boxes Nos. 2, 3, 4, 5, 6 and 12 substantially no growth was found and that the growth in boxes Nos. 7 and 11 was very insignificant, the growth in the other boxes being far more abundant. Further, it was established, quite surprisingly, that the growth in box No. 9 was comparatively most vigorous. Besides absence of weed in this box, the desired growth was thus stimulated, which was unexpected. This stimulation also occurred, though to a lesser extent, in box No. 10 which had been sprayed with a higher content of active substance (0.031 g/m^2). It should, however, be observed that an increased stimulation of the growth was not obtained solely by reducing the content of active substance sprayed, since box No. 8 whose content of active substance (0.016 g/m^2) lay between the content of box No. 10 and that of box No. 9, showed a more feeble growth than both box No. 10 and box No. 9. The stimulation of the growth would also seem to depend on the total amount of active substance and carrier sprayed, that is, on the concentration of active substance in the preparation, a preparation of lower concentration of active substance giving better growth stimulation than a preparation of higher concentration.

A further important conclusion to be drawn from Table 6 is that with a herbicidal preparation according to the invention, it is possible to use a smaller amount of active substance as compared with conventional herbicidal preparations while still obtained equally good or even better results. This entails, on the one hand, economical advantages since a smaller amount of expensive herbicide is required and, on the other hand, advantages from environmental aspects by a reduced spreading of herbicide poison. As the invention makes it possible to use extremely small amounts of active substance, it is also conceivable to make use of pesticides again which have earlier fallen into disuse because of prohibition or because a maximum limit restriction has been imposed as to their use which has been considered too low and ineffective.

TABLE 6

Box/ Square	Preparation	Active Substance + Carrier (g/m^2)	Active Substance (g/m^2)	Degree of growth Radishes	Spinach	Lettuce	Grass
1	A	0.063	0.031	+	++	±	++
2		0.313	0.156	−	−	−	+
3		1.000	0.500	−	−	−	±
4		3.000	1.500	−	−	−	±
5	B	7.500	0.750	−	−	−	±
6		2.500	0.250	−	±	−	±
7		0.825	0.082	−	+	−	++
8		0.163	0.016	++	+++	+	+++
9	C	0.625	0.006	++++	++++	++++	++++
10		3.125	0.031	+++to++++	++++	+++to+++	+++
11		10.000	0.100	−	±	±	±
12		25.000	0.250	−	−	±	±
13		0	0	+++	+++	+++	+++

− = no growth
± = weak and poor growth
\+ = irregular, but clearly discernible growth
++ = relatively good growth
+++ = good growth
++++ = excellent growth

As earlier indicated, the method according to the invention is also applicable in order to reduce the required dos of different medicines and, in some cases, make possible the utilization of medicines which have previously been considered ineffective. Thus, by way of example, tests have previously been carried out using a number of penicillin esters on rats with a view to producing an enzymatic decomposition of the ester in the digestive system and thus liberate the penicillin in active form. These experiments were successful when carried out on rats, but not on human beings for which reason it was supposed that Man lacks the capability of enzymatically breaking down the esters in question. However, by combining, according to the method of the present invention, the medicinal esters with a carrier of the type in question and in the proportions and amounts indicated, successful results may also be obtained on human beings as is apparent from the following examples. This can be ascribed partly to the medicine exposing a larger surface area partly to the fact that a considerale increase in the enzymatic reaction velocity is attaind when using the combination of the ester substrates with the respective carrier of large specific surface. As examples of antibiotic esters of the above-indicated type may be mentioned chloramphenicol esters, penicillin esters and cephalosporin esters. Two concrete examples thereof are given below.

Example 5

Chloramphenicol palmitate (2 mg/ml) and chloramphenicol palmitate applied as coat on a carrier according to the invention (Fluosil®, 200 m^2/g) in the weight ratio 50/50 (4 mg/ml) were each suspended in a solution consisting of

1 ml 1.0 M $CaCl_2$
0.1 ml Tween (Reg. Trade Mark) 80
dist. H_2O to 100 ml
5 ml 1 M Tris + HCl to pH 8.0

Each suspension was admixed with an equally large volume of a solution of pancreas lipase enzyme (from the company Sigma) (5 mg/ml) in a buffer at pH 8.0.

The preparations were tested against Escherichia coli K 12 after the enzymatic reaction was arrested by exposure to 50°C for 3 min. The results are given in Table 7.

TABLE 7

Reaction time in h for pancreas lipase	Chloramphenicol palmitate (Not coated) Inhibition zone in mm	Chloramphenicol palmitate Coated on carrier Inhibition zone in mm
0	0	0
2	0	18
4	0	17
24	0	21

It appears from Table 7 that, whereas no antibiotic effect at all was obtained with the used amounts of chloramphenicol palmitate when the antibiotic was not applied as a coat to a carrier, good antibiotic effect was obtained when the chloramphenicol palmitate was applied as a coat to a carrier of large specific surface according to the invention. As stated above, this can be explained by the fact that the enzymatic reaction velocity has increased considerably in the method according to the invention. Consequently, it would be necessary, in order to obtain the same antibiotic effect as by the method of the invention, to use a considerably larger amount in the case of the minimum dosage about twice the amount of chloramphenicol palmitate when the antibiotic is not applied as a coat to carriers according to the invention.

Example 6

The experiment according to Example 5 was repeated, use being however now made of, respectively, benzylpenicillinphenacyl ester and cephalosporinphenacyl ester as antibiotics instead of chloramphenicol palmitate and using Sarcina lutea ATCC 9341 as the test organism. Here, an inhibition zone of 12-16 mm was obtained for the antibiotic which was not applied as a coat to a carrier, while the inhibition zone for the antibiotic applied as a coat to a carrier according to the invention was 16-24 mm, that is, a distinctly improved antibiotic effect. The explanation why a certain inhibition zone was also obtained for the non-coated antibiotic is probably to be found in the presence of free benzyl penicillin on account of spontaneous hydrolysis of the phenacyl ester. Despite this side-effect, the

enhanced effect produced by the method according to the invention is however apparent.

The Examples given above for special antibiotics are not to be regarded as limitative of the invention, but many medicines, vitamins, analgesics, antibiotics, parasiticides, diabetic preparations, hormones, sedatives, anesthetics, antihistamines, mineral supplements (e.g., iron and iron compounds), anti-pyretics, prophylactics such as anti-malarials, alkaloids, antidote agents, expectorants etc, and similar substances can be better exploited when combined with a carrier of large specific surface according to the method of the invention, in that the active substances are exposed in a more effective fashion and thus give rise to a better effect than that obtained by normal dosage such that the minimum dosage of the conventional compositions is at least about 20 times greater than in the case of the present invention.

Particularly, when applied on a carrier in accordance with the invention, the biologically active substance, e.g. a medicine, is more evenly distributed and more widespread and does not produce undesired high local concentrations of the substance which may cause deleterious side effects such as gastric haemorrhage in the case of acetylsalicylic acid. In other cases, a more even and more widespread distribution of the active substance bound to a carrier with greater therapeutic effect may be obtained than when not absorbed on a carrier. This may be particularly important in the treatment of enteric infection.

Further, when the invention is used in connection with a substance that undergoes enzymatic reaction to produce a biologically active substance, i.e. a precursor for the biologically active substance (such as the esters in the above Examples 5 and 6) an enhanced liberation of the biologically active substance is obtained compared to using the substance without carrier.

Finally, it should be stressed once more that although the invention has been described particularly in connection with insecticides, herbicides and medicines, it is not restricted to these groups of substances but is applicable with biologically active substances in general to provide a predetermined biological effect using a smaller amount of biologically active substance than is conventionally used. Thus, the gist of the invention does not reside in the particular type of biologically active substance used but in the fundamental discovery that it is possible to achieve the same effect as before with the use of a smaller amount of biologically active substance if the active substance is applied in the manner previously described on a carrier with a large specific surface area in accordance with the invention.

WHAT WE CLAIM IS:-

1. A method for reducing the amount of biologically active substance required for obtaining a predetermined biological effect, comprising evenly distributing the biologically active substance or a precursor therefor, together with optional additives, on an inactive, solid, finely divided inorganic carrier having a surface area of at least 50 m^2/g in a weight ratio of from $1:10^6$ to 1:1, and selecting the dosage of the biologically active substance to be from 1/2 to 10^{-5} of the minimum dosage conventionally required to produce the same effect.

2. Method as claimed in claim 1, wherein the inorganic carrier has a surface area of at least 200 m^2/g.

3. Method as claimed in claim 1 or 2, wherein the carrier is selected from metals and metalloids, inorganic oxides, acids, salts and polymers.

4. Method as claimed in claim 1 or 2, wherein the inorganic carrier is selected from silicon dioxide and silicates.

5. Method as claimed in claim 1 or 2, wherein pyrogenic silica is used as the carrier.

6. Method as claimed in any of claims 1 to 5, wherein the carrier is neutralised by treatment with acid or alkali.

7. Method as claimed in any of claims 1 to 6, wherein the biologically active substance is distributed on the carrier in a weight ratio of from $1:10^4$ to $1:10^2$.

8. Method as claimed in any of claims 1 to 7, wherein the carrier is of a particle size of about 1-250 µm.

9. Method as claimed in any of claims 1 to 8, wherein the biologically active substance is selected from killing agents, medicines, disinfectants, biocides and deodorants.

10. Method as claimed in claim 9, wherein the killing agent is selected from insecticides, herbicides, fungicides, germicides and rodenticides.

11. Method as claimed in claim 9, wherein the medicine is selected from vitamins, analgesics, antibiotics, parasitides, diabetic preparations, hormones, sedatives, anesthetics, antihistamines, mineral supplements, antipyretics, alkaloids, antidote agents, and expectorants.

12. Method as claimed in claim 9, wherein the medicine is selected from penicillin esters, cephalosporin esters and chloramphenicol esters.

13. Method as claimed in any of claims 1 to 12, wherein the biologically active substance together with an additive is distributed on the carrier, the additive being selected from at